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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,831	12/30/2003	Richard L. Boyd	NOR-016CP2 and 286336.155	2793

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EXAMINER	
NGUYEN, QUANG	

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1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/748,831	BOYD, RICHARD L.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/24/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34, 36-43, 45-63, 65-67, 69-74, 76-78, 81, 83-88* is/are pending in the application.

4a) Of the above claim(s) *34,43,47,48,52,58,59,63,67,74,81,84 and 86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33, 36-42, 45-46, 49-51, 53-57, 60-62, 65-66, 69-73, 76-78, 83, 85, and 87-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :11/2/04;3/27/07;6/26/06;6/6/06;4/27/06;3/20/06;12/27/05;8/15/051/20/05.

DETAILED ACTION

Claims 1-34, 36-43, 45-63, 65-67, 69-74, 76-78, 81, 83-88 are pending in the present application.

Applicant's election with traverse of Group I, drawn to a method for genetically altering a subject having a T cell disorder caused by HIV infection or a patient infected with HIV or a method for treating or preventing infection of a patient by HIV, in the reply filed on 8/24/07 is acknowledged. Applicants further elected the following species: (a) Leuprolide as a species of a pharmaceutical for the disruption of sex-steroid-mediated signaling to the thymus to reactivate the thymus; (b) Genetically modified hematopoietic stem cells (HSC) as a species of administered genetically modified cells to the patient; (c) IL-7 as a species of a cytokine; and (d) a gene coding for a ribozyme that cuts HIV tat as a species of a polynucleotide expressible in genetically modified cells.

With respect to the Group restriction, the traversal is on the ground(s) that a search and examination of all of the claims of the present application would not pose an undue burden on the Examiner because all of the pending claims are classified in the same class 424, subclass 93.21. With respect to the species restriction, Applicants argue basically that members of the Markush group are sufficiently few in number so as to not constitute a serious burden on the Examiner.

This is not found persuasive because: Firstly, a search for all of the pending claimed inventions would not be limited only to a patented literature database characterized by classes and subclasses. Secondly, it would pose a serious burden for the examiner to search and examine all of the claims within a single application

because the claims are directed to distinct methods having different starting materials, different method steps and different desired results for the reasons already set forth in the Office Action mailed on 4/12/07. With respect to the species restriction, it is a serious burden on the Examiner to search all of the species of the present application and they are not few in number as asserted by Applicants (please refer to the numerous nested species recited in the claims).

The requirement is still deemed proper and is therefore made FINAL.

Claims 34, 43, 47-48, 52, 58-59, 63, 67, 74, 81, 84 and 86 were withdrawn from further consideration because they are directed to non-elected inventions and non-elected species.

Accordingly, claims 1-33, 36-42, 45-46, 49-51, 53-57, 60-62, 65-66, 69-73, 76-78, 83, 85, and 87-88 are examined on the merits herein with the aforementioned elected species.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on applications filed in Australia on 4/15/1999; 10/13/2000; 4/17/2000 and 4/18/2002. It is noted, however, that applicant has not filed certified copies of the PP9778, PR0745, PCT/AU00/00329 and PCT/AU01/01291 applications as required by 35 U.S.C. 119(b).

Claim Objections

Claim 1 is objected to because of the abbreviation "HSC" should be spelled out in full at the first occurrence of the term. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 (an embodiment), 8-9 (an embodiment), 10, 19-26, 27 (an embodiment), 55 (an embodiment), 56-57, 65-66, 69-71, 72-73, 76-78 and 85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method **for reducing or lowering HIV viral titer or infection of new cells** in a patient comprising: ablating T cells of the patient; reactivating the thymus of the patient; genetically modifying cells *in vitro* with a vector construct encoding and expressing a gene product that inhibits replication of human immunodeficiency virus;

does not reasonably provide enablement for a method for ***preventing* infection by HIV in a patient** or a method in which **administered cells are genetically modified to inhibit infection of the cells by HIV**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The instant specification is not enabled for the instant broadly claimed invention for the reasons discussed below.

1. The breadth of the claims

Claim 10 and an embodiment of claims 1, 8-9 are directed to a method for genetically altering any subject in which administered cells (hematopoieitic cells as the elected species) are genetically modified to inhibit infection of the cells by any virus.

Claims 19-26 are directed to a method for preventing infection of any patient by HIV comprising the steps of T cell ablation, disruption of sex steroid mediated signaling to the thymus, and administration of genetically modified cells selected from a Markush group recited in claim 19, with genetically modified hematopoietic stem cells as the elected species.

Claims 56-57 and an embodiment of claims 27, 27 are directed to a method for genetically altering a patient, in which administered cells are genetically modified to inhibit infection of the cells by HIV virus.

Claims 65-66 and 69-71 are directed to a method of preventing human immunodeficiency virus infection in a patient comprising the specific recited steps in independent claim 65.

Claims 72-73, 76-78 are directed to a method of treating (encompassing preventing) human immunodeficiency virus infection in a patient comprising the specific recited steps in independent claim 72.

Claim 85 is directed to a method for treating (encompassing preventing) or preventing infection by HIV in a patient comprising the specific recited steps in the claim.

2. The state of the prior art and the unpredictability of the prior art

At about the effective filing date of the present application (4/15/1999), the existence of an effective HIV vaccine was and continues to be elusive (Dropulic et al.; US 6,232,120; Boehnlein et al., US 6,776,986; Bojak et al., Drug Discovery Today 7:36-46, 2002; Mwau et al., J. Gene Medicine 5:3-10, 2003). **There are several major scientific obstacles blocking the development of a successful preventive HIV vaccine**. These include (1) the extraordinary variability of HIV strains which occur in different parts of the world over time and in patients, (2) the lack of an exact animal model of HIV-induced AIDS, and (3) the lack of understanding of correlates of positive immunity to HIV. Even in 2004, Desrosiers, R.C. (Nature Medicine 10:221-223, 2004) still state "Several lines of evidence indicate that development of an effective vaccine for HIV-1 is going to be, at best, extremely difficult. **The inability to solve fundamental scientific questions is the root cause for why a successful vaccine is not**

currently within our grasp." (abstract). Pantaleo et al. (Nature Medicine 10:806-810, 2004) also state "The lack of understanding of some crucial scientific questions (such as how to generate neutralizing antibodies), the fact that current HIV vaccine candidates may not protect from infection, and the absence of definitive experimental evidence that certain types of immune responses are indeed immune correlates of protection all favor the view that more basic research is needed before current vaccine candidates can be moved into large efficacy trials. However, it is also unclear what data from which animal model of HIV-1 infection are most relevant to human infection and vaccine protection." (page 809, col. 2, section entitled "Final considerations"). Therefore, it is apparent that the attainment of prophylactic effects against HIV infection in a human host remains elusive and unpredictable in 2004, let alone at the effective filing date of the presently claimed invention.

3. The amount of direction or guidance provided

The instant specification fails to provide sufficient guidance for a skilled artisan, including any relevant *in vivo* example (part of a guidance), on how to prevent HIV infection in any patient. There is also a lack of any teaching on how any cell is genetically modified by any vector construct such that upon administering to a treated patient the genetically modified cell itself is not infected by any virus, including the HIV virus (e.g., see the scope of claims 10, 56-57). Even with the vector construct encoding and expressing a ribozyme that cuts HIV tat, there is no evidence of record indicating that any cell, including a hematopoietic stem cell, containing this vector construct would not be infected by HIV virus, let alone by any virus. In light of the state and the

unpredictability for preventing HIV infection in a patient discussed above, coupled with the lack of sufficient guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the methods as broadly claimed.

Additionally, the courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the relevant art for attaining prophylactic effects against HIV infection *in vivo*, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the patient" in lines 3-4 of the claim. There is insufficient antecedent basis for this limitation in the claim, because prior to this limitation, there is no recitation of any patient. Accordingly, the metes and bounds of this independent claim and its dependent claims are not clearly determined.

Claim 16 recites the limitation "the method of disrupting the sex steroid mediated signaling to the thymus" in lines 1-2 of the claim. There is insufficient antecedent basis for this limitation in the claim, because prior to this limitation, there is no recitation of any disruption of sex steroid mediated signaling to the thymus, including in claim 1 which claim 16 is dependent on. Accordingly, the metes and bounds of the claim are not clearly determined.

Claim 17 recites the limitation "the pharmaceuticals" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim, because prior to this limitation, there is no recitation of any pharmaceuticals. Accordingly, the metes and bounds of the claim are not clearly determined.

Claim 18 recites the limitation "the LHRH agonists" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim, because prior to this limitation, there is no recitation of any LHRH agonist. Accordingly, the metes and bounds of the claim are not clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9, 12, 14-15, 27-33, 36-40, 53-55, 60, 83 and 88 are rejected under 35 U.S.C. 102(b) as being anticipated Sykes et al. (US 5,658,564; IDS) and evidenced by

Fredrickson et al. (Developmental and Comparative Immunology 18:251-263, 1994; IDS).

Sykes et al disclose at least a method of restoring or inducing immunocompetence in a host or recipient, including a human adult or a human child, said method comprises the steps of introducing into said host donor thymic tissue, including fetal or neonatal thymic tissue, so that host T cells can mature in the implanted thymic tissue; depleting, inactivating or inhibiting recipient natural killer cells or host T cell function (e.g., introducing antibodies capable of binding to NK cells, T cells and CD4+ cells); irradiating the recipient with low dose, whole body irradiation (e.g., subletthal irradiation, col. 28, lines 47-60); a short course of high dose immunosuppressant such as cyclosporine; as well as recipient genetically modified hematopoietic stem cells expressing a donor antigen (e.g., a donor MHC gene) to facilitate tolerance to subsequent exposure to donor antigen (see at least Summary of the Invention, particularly col. 1, line 38 continues to line 35 of col. 3 and issued claims). Sykes et al also teach the same method for treating a human at risk for an acquired immune disorder such as AIDS, patients suffering from an immunodeficiency such as a T cell deficiency, immunoincompetence resulting from a neoplastic disease or immunoincompetence resulting from a medical procedure such as chemotherapy or radiation treatment (col. 5, line 29 continues to line 19 of col. 7; col. 14, lines 29-30; coll. 15, lines 31-39).

Sykes et al further teach that due to the discovery that hematopoietic stem cells can be used to induce tolerance to a graft, they disclose a method for inducing

immunological tolerance in a recipient mammal, including a human adult or a human child, of a first species to a graft obtained from a donor mammal of a second species, said method comprises prior to or simultaneous with transplantation of the graft, introducing into the recipient mammal hematopoietic stem cells of the second species; depleting, inactivating or inhibiting recipient natural killer cells or host T cell function (e.g., introducing antibodies capable of binding to NK cells, T cells and CD4+ cells); irradiating the recipient with low dose, whole body irradiation (e.g., subletthal irradiation, col. 28, lines 47-60); and a short course of high dose immunosuppressant such as cyclosporine (col. 11, line 16 continues to line 16 of col. 13; and particularly issued claims 21-24). Sykes et al disclose that although hematopoietic stem cells drived from the graft donor are preferable, hematopoietic stem cells may be obtained from other individuals or species, or from genetically-engineered completely or partially inbred donor strains (col. 27, lines 34-37).

It should be noted that a recipient receiving donor thymic tissue, particularly fetal or neonatal thymic tissue, falls within the scope of a patient with a thymus undergoing reactivation. In addition, a recipient receiving hematopoeitic stem cells of a second species or genetically-engineered hematopoietic stem cells from a second species and undergoing whole body irradiation, would also fall within the scope of a patient with a thymus undergoing reactivation as evidenced at least by the teachings of Fredrickson et al that disclose that after sublethal irradiation thymic regeneration begins promptly and thymic cellularity is restored to near normal within 2 weeks (see at least the abstract).

Accordingly, the methods taught by Sykes et al meet every limitation of the instant broad claims. Therefore, the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 16-19, 22-27, 41-42, 45-46, 49-51 and 87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sykes et al. (US 5,658,564; IDS) and in view of Nowak, R (New Scientist 19/26, page 11, January 2, 1999; IDS), Garzetti et al. (Obstet Gynecol. 88:234-240, 1996; IDS) and Mathias, JR (US 5,434,136; IDS).

Sykes et al disclose at least a method of restoring or inducing immunocompetence in a host or recipient, including a human adult or a human child, said method comprises the steps of introducing into said host donor thymic tissue, including fetal or neonatal thymic tissue, so that host T cells can mature in the implanted thymic tissue; depleting, inactivating or inhibiting recipient natural killer cells or host T cell function (e.g., introducing antibodies capable of binding to NK cells, T cells and CD4+ cells); irradiating the recipient with low dose, whole body irradiation (e.g., subletthal irradiation, col. 28, lines 47-60); a short course of high dose immunosuppressant such as cyclosporine; as well as recipient genetically modified

hematopoietic stem cells expressing a donor antigen (e.g., a donor MHC gene) to facilitate tolerance to subsequent exposure to donor antigen (see at least Summary of the Invention, particularly col. 1, line 38 continues to line 35 of col. 3 and issued claims). Sykes et al also teach the same method for treating a human at risk for an acquired immune disorder such as AIDS, patients suffering from an immunodeficiency such as a T cell deficiency, immunoincompetence resulting from a neoplastic disease or immunoincompetence resulting from a medical procedure such as chemotherapy or radiation treatment (col. 5, line 29 continues to line 19 of col. 7; col. 14, lines 29-30; coll. 15, lines 31-39).

Sykes et al further teach that due to the discovery that hematopoietic stem cells can be used to induce tolerance to a graft, they disclose a method for inducing immunological tolerance in a recipient mammal, including a human adult or a human child, of a first species to a graft obtained from a donor mammal of a second species, said method comprises prior to or simultaneous with transplantation of the graft, introducing into the recipient mammal hematopoietic stem cells of the second species; depleting, inactivating or inhibiting recipient natural killer cells or host T cell function (e.g., introducing antibodies capable of binding to NK cells, T cells and CD4+ cells); irradiating the recipient with low dose, whole body irradiation (e.g., subletthal irradiation, col. 28, lines 47-60); and a short course of high dose immunosuppressant such as cyclosporine (col. 11, line 16 continues to line 16 of col. 13; and particularly issued claims 21-24). Sykes et al disclose that although hematopoietic stem cells drived from the graft donor are preferable, hematopoietic stem cells may be obtained from other

individuals or species, or from genetically-engineered completely or partially inbred donor strains (col. 27, lines 34-37).

Sykes et al do not teach specifically the use of Leuprolide, an LHRH agonist, (the elected species) in any of their disclosed methods for restoring or inducing immunocompetence in a treated host, including a human at risk for an acquired immune disorder such as AIDS or patients suffering from an immunodeficiency such as a T cell deficiency, immunoincompetence resulting from a neoplastic disease or immunoincompetence resulting from a medical procedure such as chemotherapy or radiation treatment.

However, at the effective filing date of the present application Nowak already reported that temporary chemical castration could help regenerate the damaged immune systems of people with HIV or who have had chemotherapy or bone marrow transplants. Nowak further disclosed that the work of Drs. Boyd and Sutherland demonstrated that upon castration, thymus of adult mice regained its youthful appearance within four weeks and the number of T cells produced increased to near pre-pubertal levels, suggesting that drugs (e.g., LHRH or luteinising hormone-releasing hormone) that suppress the production of sex steroids and partially reverse puberty might boost the immune systems of patients with AIDS or those who gave been given immunosuppressive drugs.

At the effective filing date of the present application, Garzetti et al also taught that a positive immunomodulating effect, particularly a significant progressive increase in natural killer (NK) cell activity was observed during the first 12 weeks of gonadotropin-

releasing hormone (GnRH) agonist treatment in patients with advanced endometriosis, and they proposed GnRH agonist treatment as an adjuvant medical treatment for endometriosis (see at least the abstract; page 239, col. 2, last paragraph).

Additionally, Mathias taught the use of GnRH analogs, particularly Lupron or luprolide acetate due to its increased biologic activity, stability against enzymatic degradation and high binding affinity for GnRH receptors, for alleviating the debilitating symptoms of motility disorders such as systemic lupus erythematosis, autonomic neuropathies of diabetes mellitus, sclerroderma, Parkinson's disease, functional bowel disease at least via their inhibitory activity against the production of reproductive hormones (see at least Summary of the Invention, particularly col. 3, lines 34-46 and 53-60; col. 2, lines 52-62). Mathias further disclosed that GnRH and its analogs are routinely used in the treatment of disorders of the reproductive system, including patients with endometriosis, hormone-dependent tumors such as prostatic mammary carcinomas, polycystic ovarian disease (col. 4, liens 48-62).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time of invention was made to modify a method taught by Sykes et al. by also administering leuprolide to the treated host in light of the teachings of Nowak, Garzetti et al. and Mathias.

An ordinary skilled artisan would have been motivated to carry out the above modification to enhance immunocompetence in the treated patients, particularly in human patients that are HIV positive or having AIDS. Furthermore, it is also apparent that GnRH and its analogs such as leurpolide have been used safely in humans for

various treatments. The resulting modified method is indistinguishable from the method as claimed because it has the same method steps and starting materials.

An ordinary skilled artisan would have a reasonable expectation of success because in light of the teachings of Sykes et al., Nowak, Garzetti et al. and Mathias; coupled with a high level of skill of an ordinary artisan in the relevant art.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 8-9, 11, 13, 27, 55-57, 65-66, 69-73, 76-78 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sykes et al. (US 5,658,564; IDS) and in view of Nowak, R (New Scientist 19/26, page 11, January 2, 1999; IDS), Garzetti et al. (Obstet Gynecol. 88:234-240, 1996; IDS) and Mathias, JR (US 5,434,136; IDS) as applied to claims 1, 16-19, 22-27, 41-42, 45-46, 49-51 and 87 above, and further in view of Dropulic et al. (US 6,232,120 B1).

The combined teachings of Sykes et al., Nowak, Garzetti et al. and Mathias were already presented above. However, none of the references teaches specifically using hematopoietic stem cells genetically modified with a gene that inhibits infection, replication or function of human immunodeficiency virus, particularly a gene coding for a ribozyme that cuts HIV tat gene (elected species), and further treating the patient with anti-retroviral therapy, particularly highly active retroviral therapy.

However, at the effective filing date of the present application Droulic et al already taught a method for inhibiting the replication of an infective replicable human

immununodeficiency virus (HIV) in a cell, including a stem cell (at least col. 20, lines 46—58), in a patient or *in vivo* by contact the cell *ex vivo* which is infected or at risk of being infected with the HIV virus with a conditionally replicating recombinant viral vector encoding and expressing a ribozyme targeting a wild type HIV genome, including a triple anti-Tat ribozyme cassette, wherein the catalytic domain of each ribozyme of the triple ribozyme cassette cleaves a different site on a wild-type human HIV nucleic acid molecule (col. 15, line 56 continues to line 11 of col. 16), then return of the genetically modified cell to the patient (see at least col. 23, line 9 continues to line 53 of col. 24; issued claims, particularly claims 24 and 30). Dropulic et al further taught that treated patients could also be subjected to other conventional treatments, including administration of anti-retroviral agents such as RT inhibitors, such as ddC, zidovudine, ddI, ddA or other inhibitors that act against other HIV proteins, such as anti-TAT agents (highly active retroviral therapy); as well as administration of immunomodulators and immunostimulants such as various interleukins, CD4, cytokines, blood transfusion and cell transfusions, antifungal and antibacterial agents (col. 27, line 54 continues to line 46 of col. 28).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time of the invention was made to further modify a method taught by Sykes et al., Nowak, Garzetti et al. and Mathias by further genetically modifying transplanting hematopoieitc stem cells in patients having or at risk of HIV infection with a conditionally replicating recombinant viral vector encoding and expressing a ribozyme targeting a wild type HIV

genome, including a triple anti-Tat ribozyme cassette, in light of the teachings of Dropulic et al.

An ordinary skilled artisan would have been motivated to carry out the above modification to reduce or limit wild-type HIV pathogenicity or at least to reduce HIV virus load burden in a patient having or at risk of HIV infection by the approach successfully taught by Dropulic et al.

An ordinary skilled artisan would have a reasonable expectation of success because in light of the teachings of Sykes et al., Nowak, Garzetti et al., Mathias and Dropulic et al., coupled with a high level of skill of an ordinary artisan in the relevant art.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 27 and 61-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sykes et al. (US 5,658,564; IDS) and in view of Bolotin et al. (Blood 88:1887-1894, 1996; IDS).

The teachings of Sykes et al. were disclosed above. Sykes et al do not teach specifically a further step of administering IL-7 (the elected species) in any of their disclosed methods.

However, at the effective filing date of the present application Bolotin et al already taught that IL-7 administration promotes thymic reconstitution and enhanced thymopoiesis after bone marrow transplantation (BMT) and is useful in preventing post-bone marrow transplantation immune deficiency (see at least the abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time of invention was made to modify a method taught by Sykes et al. by further administering IL-7 into the treated host in light of the teachings of Bolotin et al.

An ordinary skilled artisan would have been motivated to carry out the above modification to enhance thymopoiesis and thereby enhancing immunocompetence in the treated patients.

An ordinary skilled artisan would have a reasonable expectation of success because in light of the teachings of Sykes et al. and Bolotin et al., coupled with a high level of skill of an ordinary artisan in the relevant art.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 7, 14-19, 22-33, 36-37, 39-42, 45-46, 49-51, 60-62, 83 and 87-88 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-20, 23, 25, 28-31, 34-36, 36-40, 55, 57-60, 62, 64-65 of copending Application No. 10/749,119.

Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are directed to a method for genetically altering a subject comprising the steps of genetically modifying cells from a recited Markush group of cells, and delivering them to the subject while the subject's thymus is undergoing reactivation or a method for preventing infection of a patient by HIV having the specific steps recited in independent claim 19 or a method for genetically altering a patient having the specific steps recited in independent claim 27. Claims 19-20, 23, 25, 28-31, 34-36, 36-40, 55, 57-60, 62, 64-65 of copending Application No. 10/749,119 are drawn to a method for inducing tolerance in a patient to a graft from a mismatched donor, comprising the steps of depleting T cells of the patient or providing the patient with immunosuppressive therapy, reactivating the thymus of the patient and administering cells from the mismatched donor to the patient, wherein the cells being selected from the group consisting of stem cells, progenitor cells, dendritic cells, and combinations thereof.

The claims of the present application differ from the claims of the co-pending application in reciting "genetically modifying cells, wherein the cells are selected from HSC". The claims of the present application can't be considered to be patentably distinct over claims 19-20, 23, 25, 28-31, 34-36, 36-40, 55, 57-60, 62, 64-65 of

copending Application No. 10/749,119 when the scope of independent claim 19 encompasses specifically hematopoietic stem cells (dependent claim 28) and genetically modified cells from a mismatched donor (dependent claim 60), and therefore they fall within the scope of claims 1-5, 7, 14-19, 22-33, 36-37, 39-42, 42-46, 41-51, 60-62, 83 and 87-88 of the present application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-9, 14-19, 22-33, 36-42, 45-46, 49-51, 60-62, 83 and 87-88 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-33, 36-42, 45-50, 80-82, 92-98 of copending Application No. 10/749,118.

Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are directed to a method for genetically altering a subject comprising the steps of genetically modifying cells from a recited Markush group of cells, and delivering them to the subject while the subject's thymus is undergoing reactivation or a method for preventing infection of a patient by HIV having the specific steps recited in independent claim 19 or a method for genetically altering a patient having the specific steps recited in independent claim 27. Claims 19-20, 23, 25, 28-31, 34-36, 36-40, 55, 57-60, 62, 64-65 of copending Application No. 10/749,118 are drawn to a method for treating or alleviating symptoms of an autoimmune disease in a patient having or suffering an autoimmune disease, comprising: depleting T cells in the patient;

and reactivating the thymus of the patient, wherein the patient has an improved prognosis for the autoimmune disease compared to an untreated patient suffering from the autoimmune disease.

The claims of the present application differ from the claims of the co-pending application in reciting "genetically modifying cells, wherein the cells are selected from HSC...., and delivering them to the patient". The claims of the present application can't be considered to be patentably distinct over claims 29-33, 36-42, 45-50, 80-82, 92-98 of copending Application No. 10/749,118 when the scope of independent claim 29 encompasses specifically the step of further administering cells to the patient, wherein the cells are stem cells, including hematopoietic stem cells (dependent claims 32-33) and the administered stem cells are genetically modified (dependent claim 93), and therefore they fall within the scope of claims 1-9, 14-19, 22-33, 36-42, 45-46, 49-51, 60-62, 83 and 87-88 of the present application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

At the effective filing date of the present application, Nabel et al (US 5,650,306) already taught a method for treating individuals infected with HIV by introducing into them transfected cells, including transfected hematopoietic stem cells, comprising a recombinant nucleic acid molecule encoding a gene product that inhibits the expression

of HIV genes, such as mutants of the rev and gag genes, ribozymes, antisense nucleic acids inhibiting HIV gene expression (see at least Summary of the Invention and issued claims 9-10).

Additonally, Bochnlein et al. (US 6,776,986) also disclosed a successful method for inhibiting HIV-1 replication in a CD4+ or hematopoietic stem cell in an HIV-1 infected patient (see at least issued claims 28-30 and Summary of the Invention).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

QUANG NGUYEN, PH.D.
PRIMARY EXAMINER